Prevalence of Obstructive Sleep Apnea in Joint Hypermobility Syndrome: A Systematic Review and Meta-Analysis

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Abstract: STUDY OBJECTIVES: Because of associated abnormalities affecting connective tissue in various organs including airways, hypermobility syndrome has been associated with high risk for the development sleep apnea. Ehlers-Danlos syndrome (EDS) and Marfan syndrome (MFS) represent the most common hypermobility syndromes; therefore, the purpose of this review was to examine the prevalence of obstructive sleep apnea (OSA) in these populations. METHODS: All publications and poster presentations written in English found through August 2018 that describe the prevalence of sleep apnea among people with EDS or MFS were included. RESULTS: A total of 13 studies were identified, 7 for EDS and 6 for MFS. A combined random prevalence rate of OSA across both populations was 48.9% (95% confidence interval 38.3-59.6), with a slightly higher rate of 59.7% (39.7-77.0) for MFS versus 39.4% (28.8-51.1) for EDS. However, a high degree of heterogeneity across studies was found in both groups (EDS group: Q = 28.6 and I2 = 79.0; MFS group: Q = 37.1 and I2 = 86.5). When directly compared to the general population, patients with EDS/MFS were on average six times more likely (odds ratio 6.28 [95% confidence interval 3.31-11.93], $P < 0.001$, Z = 5.61) to have a diagnosis of OSA. CONCLUSIONS: OSA is a previously underestimated EDS/MFS-related complication. The high prevalence of OSA might be the result of bony and soft-tissue abnormalities associated with these hypermobility syndromes. Untreated OSA is thought to worsen cardiovascular complications especially among those with MFS. Further research is needed to better delineate whether the prevalence of OSA is moderated by factors such as sex, body mass index, bony structure, and disorder subtype.

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REVIEW ARTICLES

Prevalence of Obstructive Sleep Apnea in Joint Hypermobility Syndrome: A Systematic Review and Meta-Analysis

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Study Objectives: Because of associated abnormalities affecting connective tissue in various organs including airways, hypermobility syndrome has been associated with high risk for the development sleep apnea. Ehlers-Danlos syndrome (EDS) and Marfan syndrome (MFS) represent the most common hypermobility syndromes; therefore, the purpose of this review was to examine the prevalence of obstructive sleep apnea (OSA) in these populations.

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Results: A total of 13 studies were identified, 7 for EDS and 6 for MFS. A combined random prevalence rate of OSA across both populations was 48.9% (95% confidence interval 38.3–59.6), with a slightly higher rate of 59.7% (39.7–77.0) for MFS versus 39.4% (28.8–51.1) for EDS. However, a high degree of heterogeneity across studies was found in both groups (EDS group: Q = 28.6 and I^2 = 79.0; MFS group: Q = 37.1 and I^2 = 86.5). When directly compared to the general population, patients with EDS/MFS were on average six times more likely (odds ratio 6.28 [95% confidence interval 3.31–11.93], $P < 0.001$, Z = 5.61) to have a diagnosis of OSA.

Conclusions: OSA is a previously underestimated EDS/MFS-related complication. The high prevalence of OSA might be the result of bony and soft-tissue abnormalities associated with these hypermobility syndromes. Untreated OSA is thought to worsen cardiovascular complications especially among those with MFS. Further research is needed to better delineate whether the prevalence of OSA is moderated by factors such as sex, body mass index, bony structure, and disorder subtype.

Keywords: connective tissue disease, Ehlers-Danlos, Marfan syndrome, hypermobility syndrome, sleep apnea

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INTRODUCTION

Hypermobility syndrome is characterized by joint hypermobility, usually with the involvement of organs in the body. It is usually a genetic or inheritable disease transmitted through an autosomal dominant or recessive gene. Hypermobility syndrome includes several specific disorders affecting different types of collagen in the body, including Ehlers-Danlos syndrome (EDS), Marfan syndrome (MFS), osteogenesis imperfecta (OI), and other rare syndromes (eg, pseudoxanthoma elasticum, cutis laxa syndrome, ectopia lentis syndrome, Weill-Marchesani syndrome, and Shprintzen-Goldberg syndrome). In addition, hypermobility syndrome can occur in people with chromosomal abnormalities with high OSA risk (eg, Down syndrome[1]) or metabolic diseases (eg, homocystinuria and hyperlysinemia). Joint pain, dislocation and recurrent injuries, dizziness, excessive daytime sleepiness, and fatigue can be associated with hypermobility syndrome. The nine-point Beighton scale is used to screen for suspected cases of hypermobility.[2] People with EDS are at potentially increased risk for OSA due to cartilaginous defects, chest deformities, scoliosis, dilated aorta causing tracheal compression, and vocal cord abnormalities.[3] EDS affects 1.5 million people worldwide, with an overall prevalence of 1 in 5,000 births but affecting more females than males.[4] There are 13 different subtypes.[5] MFS affects collagen as well, but with patients usually presenting as tall, and with long and slender fingers and toes. The prevalence of the disorder is thought to be between 6.5 to 20 per 100,000.[6] Although most MFS cases are due to a mutation of the *fibrillin-1* gene on chromosome 15q21, a small number (less than 10%) lack this mutation. Revised Ghent criteria are usually used to diagnose MFS.[7] Tall and thin stature, scoliosis or kyphosis, high arched plate, and mandibular retrognathia are usually causes for increased risk of OSA.

Although there are multiple collagenic diseases that present with joint hypermobility, research examining OSA prevalence has focused on EDS and MFS. Thus, due to this limitation, the current systematic review focuses on these two types of hypermobility syndrome. Because prevalence of OSA varied among studies, our purpose is to evaluate the prevalence of OSA among both EDS and MFS and examining moderators possibly affecting the prevalence; in addition, examining difference among common subtypes of EDS. It is of importance that OSA be diagnosed and effectively treat the disorder given its suggestive association with worsening of cardiovascular conditions (ie, abdominal aneurysm enlargement).

Table 1—EDS and OSA.

Study	Country (year)	Study Population	OSA	Study Type	Referral Source	Age (years)	Sex (%F)	BMI (kg/m²)	AHI (events/h)	HST/PSG
Babcock et al.	United States (2018)	596 children and adults (100% hypermobility)	46.48% had SDB (HST or PSG), 32.21% OSA, and 9.90% UARS	Retrospective (2016–2017)	Neurology clinic	Mean ± SD (range) 36 ± 12.6 (9–71)	90%	Unknown	Unknown	HST & PSG
Domany et al.	United States (2018)	65 children (100% hypermobility)	26% OSA	Retrospective (2009–2017)	Sleep clinic with sleep complaint	Mean ± SD 13.15 ± 3.9	67.7%	Median (range) 21.06 (17.9–4.4)	Unknown	PSG
Gaisl et al.	Switzerland (2017)	100 adults (46% hypermobile, 35% classical and 19% other)	32% OSA	Prospective	EDS database and community random sample (comparison group)	Mean ± SD 39.9 ± 12.8	82%	Mean ± SD 24.4 ± 5.6	Median (range) 2.9 (1.3–7.6)	HST
Gaisl et al.*	Switzerland	29 adults	27.6% OSA	Prospective	Community		79.6%	Unknown	Unknown	Unknown
Guilleminault et al.	France (2013)	34 consecutive patients, children and adults	100% OSA	Retrospective	Sleep clinic with sleep complaint	Range 7–52	55.9%	Mean ± SD 23.3 ± 2.1	Median (range) 14.21 (5.1–38)	PSG
Schultz et al.	United States (2017)	27 consecutive patients with hypermobility, children and adults	70% OSA	Retrospective	Sleep clinic	Mean ± SD 33.1 ± 16	76%	Mean ± SD 25.3 ± 5.8	Mean ± SD 11.6 ± 11.5	PSG
Stoberl et al.	Switzerland (2017)	24 children (AHI > 1 event/h)	42% (compared to 13%)	Prospective	Community	Range 6–18	Unknown	Unknown	Median 0.77	HST

* = unpublished study. AHI = apnea-hypopnea index, BMI = body mass index, EDS = Ehlers-Danlos syndrome, HST = home sleep test (in-home), OSA = obstructive sleep apnea (AHI at least 1 event/h in children and adolescents and more than 5 events/h in those older than 18 years), PSG = polysomnography (in-laboratory), SD = standard deviation, SDB = sleep-disordered breathing (includes primary snoring, UARS, and OSA), UARS = upper airway resistance syndrome.

METHODS

Study Selection and Data Extraction

A literature review using PubMed, Google Scholar, PLOS, and Ovid was conducted through August 2018. Published articles and/or posters written in English were identified by searching for "Ehlers-Danlos syndrome" or "Marfan syndrome" crossed by "obstructive sleep apnea," "apnea," or "polysomnography." Studies using both in-laboratory and in-home sleep studies were included. However, those based on questionnaires obtained from individuals were excluded because there is a lack of reliability in diagnosing OSA through self-reports.[8,9]

Statistical Analysis

Data were analyzed using the Comprehensive Meta-analysis version 2 program to estimate the prevalence of OSA in both EDS and MFS. To quantify the amount of dispersion between studies, both Cochran Q and I^2 are reported, with 25%, 50%, and 75% representing small, moderate, and high levels of heterogeneity, respectively, for I^2. In addition, although the modest number of studies does not allow for formal examination of moderators that might affect prevalence, study characteristics such as sex, age, type of EDS, body mass index (BMI), and country where the study was conducted, in addition to prevalence, were tabled whenever possible.

RESULTS

Study Extraction

Nine studies were found to assess the prevalence of OSA in patients with EDS,[8,10–17] whereas 13 studies were found for patients with MFS. Among the EDS studies, four were posters, three of which had overlapping subjects as confirmed by contacting the study authors. Accordingly, the study with the greater sample was included.[10–12] Two other publications used self-reports to assess OSA and were thus eliminated.[8,12] Finally, unpublished data were available by Gaisl and colleagues; thus, a total of seven EDS studies (four published articles, two posters, and one unpublished data set) representing 875 individuals were included in the final analysis[10,11,13–17] (**Table 1**). In the MFS group, 7 of 13 identified studies were excluded for the following reasons: being a case report,[18–20] being part of a larger study,[21,22] or reporting on only individuals with severe OSA for surgery and thus representing a significant selection bias.[23,24] Thus, the MFS sample included the remaining 6 studies, representing a total of 282 individuals with MFS[25–30] (**Table 2**).

OSA Prevalence

The prevalence of OSA among people with EDS was 39.4% (95% confidence interval [CI] 28.8–51.1, P = .08). In contrast, the prevalence rate among those with MFS was 59.7% (39.7–77.0, P = 0.94). In the EDS group, Q = 28.6 and I^2 = 79.0, compared to the MFS group, where Q = 37.1 and I^2 = 86.5 suggesting high heterogeneity rate in both groups. The combined 13 studies' prevalence rate was 48.9% (95% CI 38.3–59.6), Q = 82.4 and I^2 = 85.4 (**Figure 1** and **Figure 2**).

Age Group and OSA Prevalence

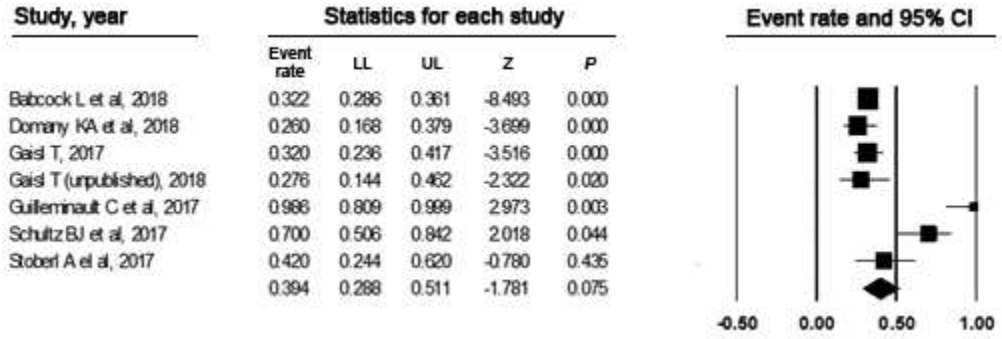
To examine whether prevalence varies among children and adults, separate analyses were conducted for each age group. In the EDS group, one study included both children and adults,[14] whereas two others reported mean ages but failed to specify age range and were thus excluded.[10,13] Thus, two studies included children totaling 89 children[16,17] and one study included 100 adults.[15] There was no observable difference in OSA in children

Table 2—MFS and OSA.

Authors	Country (year)	Study Population	SDB	Study Type	Referral Source	Age (years)	Sex (%F)	BMI (kg/m²)	AHI (events/h)	HST/PSG
Cistulli et al.	Australia (2000)	15 consecutive adults	86.67%	Prospective	Community	Mean ± SD 34.8 ± 13.2	60%	Unknown	Mean ± SD 19 ± 15	PSG
Cistulli et al.	Australia (1993)	25 adults	64%	Prospective, case control	Community	Mean ± SD 31.9 ± 2.8	52%	Unknown	Mean ± SD 13.76 ± 3	PSG
Kohler et al.	Switzerland (2009)	61 adults; 26 in comparison group	32.8% (mild 14.75%, mod/ severe 18.03%)	Prospective	Community	Mean ± SD 38.3 ± 12.9	60.66%	25.1 ± 5.9	Median (range) 5.5 (0.9–13.9)	HST
Paoloni et al.	Italy (2018)	20 children	80%	Prospective (2015–2017)	Community	Mean ± SD 8.5 ± 1.7	60%	Unknown	Unknown	HST
Rybczynski et al.	Germany (2010)	68 adults	30.88% OSA (mild in 21% and moderate in 7.35%, severe 2.95%)	Prospective	Community/ MFS clinic	Mean ± SD (range) 41 ± 14 (18–70)	51.47%	22 ± 4	Unknown	HST
Sowho et al.	United States (2018)	49 adults	69%	Prospective	Community (through the annual Marfan Foundation)	Mean ± SD 51.8 ± 13.4	57.14%	27.2 ± 6.3	Unknown	HST

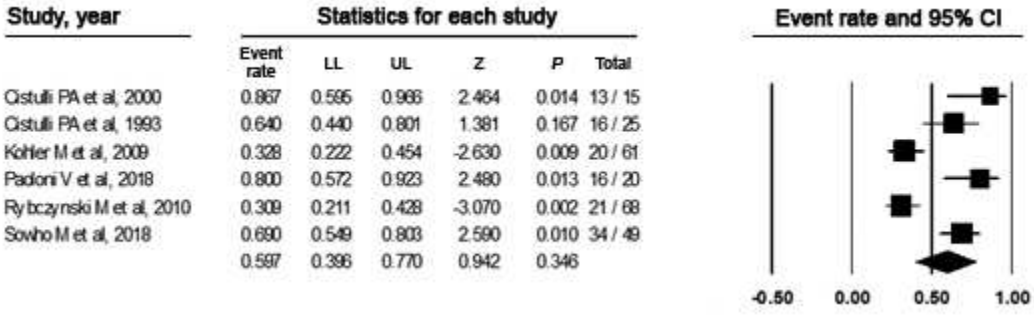
AHI = apnea-hypopnea index, BMI = body mass index, HST = home sleep test (in-home), MFS = Marfan syndrome, OSA = obstructive sleep apnea (AHI at least 1 event/h in children and adolescents and more than 5 events/h in those older than 18 years), PSG = polysomnography (in-laboratory), SD = standard deviation, SDB = sleep-disordered breathing (includes primary snoring, UARS, and OSA), UARS = upper airway resistance syndrome.

Figure 1—Prevalence rate of OSA among EDS population.



Event rate is the percentage of OSA in the group, with overall event rate of 0.39 or 39%. Lower limit versus upper limit is range where prevalence of OSA in EDS would occur. *P* value is whether this relationship occur by chance or not. CI = confidence interval, EDS = Ehlers-Danlos syndrome, LL = lower limit, OSA = obstructive sleep apnea, UL = upper limit.

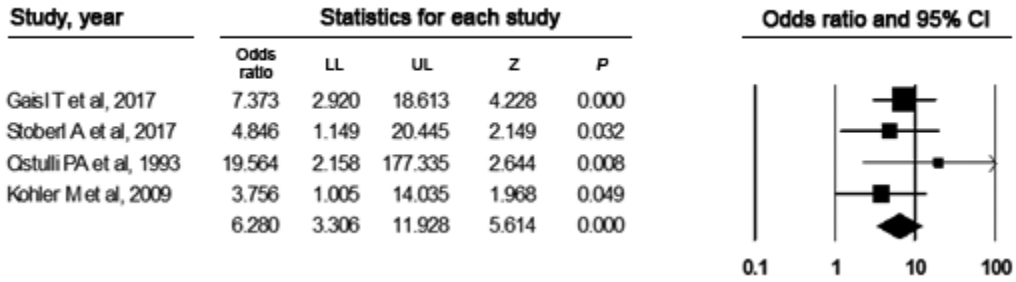
Figure 2—Prevalence rate of OSA among MFS population.



Event rate is the percentage of OSA in the group, with overall event rate of 0.597 or 60%. Lower limit versus upper limit is range where prevalence of OSA in EDS would occur. *P* value is whether this relationship occur by chance or not. CI = confidence interval, LL = lower limit, MFS = Marfan syndrome, OSA = obstructive sleep apnea, UL = upper limit.

(prevalence ranging from 26% to 42%; weighted average rate was 32.1% [95% CI 19.1–48.8; $P = .04$])[16,17] versus adults (weighted average prevalence of 31% [23.7–39.5; $P < .001$]).[15] In the MFS group, only one study included both children and adults (using an apnea-hypopnea index [AHI] cutoff of 5 events/h) but reported subgroups of child patients with OSA using different AHI cutoffs (other studies used AHI > 1 event/h in children and > 5 events/h in adults).[30] Thus, this study with a modest sample was divided into children in whom OSA was diagnosed using an AHI cutoff > 1 event/h (n = 7; OSA was 57.1%) and adults using AHI cutoff > 5 events/h (n = 18; OSA was 72.22%). Among the two child studies (n = 27), OSA prevalence was 72.3% (95% CI

Figure 3—Combined comparison of EDS and MFS versus controls.



Odds ratio is the increased probability of OSA occurring in EDS/MFS individuals versus controls, an odds ratio of 6.28 is noticed. Lower limit versus upper limit is range where prevalence of OSA in EDS would occur. *P* value is whether this relationship occur by chance or not. CI = confidence interval, EDS = Ehlers-Danlos syndrome, LL = lower limit, MFS = Marfan syndrome, OSA = obstructive sleep apnea, UL = upper limit.

47.8–88.2). In contrast, the prevalence rate (57.3% [35.3–76.7]) was lower among the five adult studies (n = 218).

Referral Source and OSA Prevalence

One would expect a higher prevalence of OSA to be reported among individuals presenting at a sleep clinic compared to those from community settings or clinics specializing in hypermobility disorders. Accordingly, we examined the effects of excluding individuals with EDS or MFS who may have been recruited from a sleep clinic on OSA prevalence rates. Three studies among the EDS group were unclear as to whether their sample was from a sleep clinic or another setting. Among the three studies that clearly were not from sleep clinics (in addition to the unpublished study),[10,15,17] OSA prevalence ranged from 32.0% to 42.0% (average prevalence rate = 32.3%; $P < .001$), somewhat lower than the rate reported when including all studies, but still much higher than in general community samples of individuals without EDS. A more variable prevalence, ranging from 26.0% to 100%, was found among the three remaining studies that potentially included individuals from sleep clinics (average prevalence rate = 70.6%; $P = .40$).[13,14,16] In contrast, each study of individuals with MFS appears to have evaluated them from community or other samples that did not include sleep clinics, thus minimizing concerns about selection bias of the MFS samples in estimating OSA prevalence.

Study Country and OSA Prevalence

Of note, among the included studies in the EDS group, three were from the United States (n = 596, 65 and 27 across the three studies), three from Switzerland (n = 100, 24 and 29) and one from France (n = 34). Those from the United States had a prevalence ranging from 26% to 70%, whereas those from Switzerland ranged from 27% to 42%, whereas the one study from France reported 100% OSA prevalence. This latter study had a modest sample size (n = 34) and, perhaps more importantly, was performed with patients with EDS who were referred to a sleep clinic, which likely explains the exceptionally high prevalence of OSA in their sample. More broadly, the different prevalence rates of OSA across countries may be related to the use of different scoring systems across countries. In the MFS group, two studies were from Australia (n = 25 and 15), and one each from Italy (n = 20), Germany (n = 68), Switzerland (n = 61), and the United States (n = 49). Italy, the United States, and Australia had the highest prevalence, ranging from 70% to 86%, compared to the other countries where prevalence was 21% to 34%.

OSA Severity

Analyzing the severity of OSA in EDS, based on one study including 100 adult individuals, 21% had mild (AHI 5 to < 15 events/h), 11% moderate (AHI 15 to < 30 events/h), and 4% severe (AHI ≥ 30 events/h) OSA.[15] Among adults with MFS, three studies showed mild OSA occurring in 15% to 28% of individuals as categorized by AHI cutoffs ranging from 5 to < 15 events/h, whereas 7% to 20% of individuals exhibiting moderate OSA (AHI 16 to < 30 events/h) and 3% to 16% of individuals exhibiting severe OSA (AHI ≥ 30 events/h) in 3% to 16%.[25,26,30] Among 25 individuals with MFS, 28% (n = 7) had mild OSA, 20% (n = 9) had moderate OSA, and 16% (n = 4) had severe OSA.[30] In another study by Rybczynski and colleagues that included 68 individuals with MFS, 21% (n = 14) had mild OSA, 7% (n = 5) moderate OSA, and 3% (n = 2) had severe OSA.[25] In the third study by Kohler et al. that included 61 individuals with MFS, 15% (n = 9) had mild OSA, 11% (n = 7) had moderate OSA, and 6.5% (n = 4) had severe OSA.[26]

OSA Prevalence in EDS and MFS Compared to Controls

There were four studies, two in each group, that compared the prevalence of OSA to control patients without a hypermobility disorder (**Table 1** and **Figure 3**). An OR of 6.28 (95% CI 3.31–11.93, $P < .001$, Z = 5.61) was found, suggesting that individuals with EDS or MFS are six times more likely than those without a hypermobility disorder to have OSA. The *Q* value in these studies was 1.85 and $I^2 < 0.0001$. In the two studies of individuals with EDS, the OR was 6.52 ($P < .0001$, Z = 4.72, *Q* value = 0.23 and $I^2 < 0.0001$). Similarly, in the two studies of individuals with MFS, the OR was 6.70 ($P = .016$, Z = 2.42 and *Q* value = 1.59 and $I^2 = 36.95$).

DISCUSSION

Although the prevalence of OSA in both EDS and MFS varied among studies, a consistently high prevalence (ranging between

26% and 100%) was found compared to the rates typically reported for community samples. The estimated prevalence of OSA in community samples typically ranges from 0.7% to 3.3%, although a recent systematic review suggested a higher range from 9% to 38% among adults using an AHI cutoff of 5 events/h,[31–34] still lower than rates found for EDS and MFS in our analysis. Overall, we found prevalence rates of 39.4% and 59.7% for EDS and MFS, respectively. Although a higher prevalence of OSA was found in EDS population referred to the sleep clinic versus the community sample (70.6 versus 32.3 respectively), they were both elevated. Such elevated rates highlight the importance of evaluating OSA in these two populations of individuals with a hypermobility disorder.

In general community samples, males and obese individuals have elevated risk for OSA. Although not examined in most studies, one study did report that individuals with obesity and males with OSA were at increased risk for OSA than either nonobese and female individuals with EDS, consistent with community samples.[15] This finding supports a significant role of classical risk factors in the EDS population. Examining child studies, some evidence of possible moderation was found as higher rates of OSA were found among adults than children, but this finding needs to be tempered by the very modest sample size of the one study examining both age groups, as well as the presence of different AHI cutoffs for children.[30] In contrast, the prevalence of OSA appears to be very similar among children and adults with EDS based on the limited data.

There are several potential causes for these high rates of OSA among individuals with hypermobility disorders. First, the abnormal collagen quality that is present in the airway leads to increased nasal airway resistance and collapse. Patients with both disorders have chest (pectus) as well as spinal cord (ie, scoliosis and kyphosis) deformities have increased OSA prevalence. In addition, there is evidence that craniofacial abnormalities (high-arched palate and mandibular retrognathia) might contribute to high OSA prevalence in patients with MFS.[26] This is in contrast to individuals with EDS, for whom craniofacial phenotyping (based on a computer algorithm, which is usually used in risk stratification for OSA patients in sleep clinics) has been found to indicate no abnormalities when compared to the general population.[15,35] Regarding OSA risk due to obesity, people with MFS are usually tall and slim. One study suggested that the effect of the hypermobility syndrome is comparable to a +11 kg/m^2 BMI gain in the normal population[15]. Lung abnormalities, including higher prevalence of sinusitis, tracheomegaly and increased gas transfer coefficient have also been observed in EDS population.[36]

There were two studies comparing age- and sex-matched patients with EDS and control patients, both conducted in Switzerland by the same group. In the child and adolescent sample, OSA prevalence was found to be 43% compared to the control group at 13%. In the adult-based study, the prevalence of OSA in the EDS group was 32% compared to 6% in the comparison group. These rates are lower than the overall prevalence found in our meta-analysis, possibly due to the small number of individuals enrolled in the study (24 in the children and adolescent study versus 100 in the adult group), but further support the conclusion that individuals with hypermobility disorders are at increased risk of OSA. Although there was a higher prevalence of OSA in the child group compared to adults, it is not clear if the larger airway might decrease the prevalence. EDS has 13 different subtypes; although the prevalence of OSA among different subtypes are not well studied, one study examined prevalence among classic, vascular, hypermobility, and other subtypes and found no difference in prevalence or mean AHI (11% among classical and vascular subtypes and 14% among each of the hypermobility and unknown types).[14] Similarly, two studies were found to include individuals with MFS: a study involving 25 children found a prevalence of 64.0% versus 8.3% in the control group including 12 counterparts.[24] Similarly, the prevalence of OSA in adults with MFS showed a rate of 32.8% versus 11.5% in controls (61 were in MFS group versus 26 controls).[26] However, these studies were less well controlled compared to the EDS studies. Constriction of the maxillary arch (high arched palate) and increased nasal airway resistance was found in the MFS group compared to the control groups.[22–24]

The high prevalence of OSA in patients with hypermobility may contribute to significant adverse health outcomes in this population. Patients with MFS and EDS already report lower levels of quality of life and higher rates of excessive daytime sleepiness when compared to the general population.[8,15] OSA is a well-known underlying cause of impaired quality of life, fatigue, and daytime sleepiness and in one study the OSA severity was positively associated with lower quality of life.[15] In addition, several studies suggested a higher prevalence of cardiovascular complications in untreated patients with OSA.[37–39] This is especially applicable in patients with MFS in which suggested higher rate of aortic dissection with higher AHI,[37] faster aortic artery dilatation expansion rate in those with high oxygen desaturation index above 30 events/h compared to those with lower levels[38] and decreased progression of aortic root dilatation with the use of continuous positive airway pressure to treat the associated OSA.[39] This is probably related to the sympathetic hyperactivity and increased arousal caused by OSA increasing blood pressure, leading to increased shearing effect on vessels and endothelial dysfunction.[40] Similar mechanisms and observations have been observed in the general population.[41]

Studies examining the sensitivity and specificity of home sleep studies versus in-laboratory studies suggest the latter should be used in the EDS and MFS populations to most accurately detect OSA cases.[10] This is in comparison with the general adult population in which in-home sleep studies are usually recommended. A four-fold increase in OSA diagnostic sensitivity was found with in-laboratory compared to in-home testing in one study.[11] These authors found an unusually high number of inconclusive results from in-home testing (71 inconclusive cases out of 123 who have in-home studies, or 58%). Given the high number of inconclusive cases who had to repeat the study as well as still-suspected cases of OSA among those who tested negative for OSA (ie, possible false negatives) lead clinicians to frequently order in-laboratory studies after already conducting in-home studies.[11] Thus, conducting the initial tests in-laboratory rather than in-home can lead to a quicker time to diagnosis, as well as avoiding a possible high dropout rate for those patients who are asked to complete two

different types of sleep studies. The exceptionally high sensitivity rate with the in-laboratory testing might be explained by the high pulmonary and cardiovascular complications found among those with hypermobility syndromes. Previous studies have recommended the use of in-laboratory testing rather than in-home testing for individuals with pulmonary, neuromuscular disease or cardiovascular complications in the general population (ie, without hypermobility syndrome) due to its increased diagnostic accuracy among these populations.[42] Moreover, in the adult population without hypermobility syndrome, untreated OSA has been associated with a variety of medical conditions including obesity, hypertension, diabetes mellitus, and strokes. Although it is less studied in hypermobility syndrome, some studies suggest a worsening of vascular abnormalities in the MFS group, thus highlighting the importance of accurately diagnosing and treating this condition.[37–39]

The current review and meta-analysis has several limitations. First, the identified studies generally include a small number of participants, which may in part explain the high degree of variability in OSA prevalence rates across some studies. In addition, most studies did not examine the subtypes of the disorders or presence of other craniofacial measurements that can significantly affect the prevalence. Second, selection bias was not clearly delineated in some studies. Nonetheless, even when excluding studies that appear to have used sleep clinic populations, the prevalence of OSA was still very high among those with EDS and MFS. Third, due to the rarity of other hypermobility syndrome cases, we could not find sufficient research assessing the prevalence in these disorders (eg, pseudoxanthoma elasticum, cutis laxa syndrome, ectopia lentis syndrome, Weill-Marchesani syndrome, and Shprintzen-Goldberg syndrome). Fourth, these studies assess a point prevalence of the disorder; it is not clear whether OSA develops early in the disease (ie, during childhood), with the narrow airway compared to adults worsening the condition or the possibility that time and strain over the abnormal collagen would lead to worsening of OSA with age. Although the latter might be more expected and substantiated by the higher prevalence of OSA in the adult group compared to child with EDS (in children, prevalence ranged from 26% to 42% compared to adults ranging from 42% to 100%), this did not appear to be the case for MFS (children prevalence was 80% compared to the adults at 31% to 69%). However, the small sample size and selection bias makes it difficult to draw any conclusions. In addition, it is not clear if upper airway exercise might affect the OSA prevalence in this population. This contradicts with the results from a study conducted by Rybczynski et al., in which older age and high BMI were associated with higher AHI.[25] Fifth, the definition and criteria for an OSA diagnosis has varied over the years: although most studies have used an AHI of 5 events/h as a cutoff, others have also included oxygen desaturation index as a measure, thus possibly underestimating the prevalence. Last, this study focused on OSA and did not access for central apneas nor upper airway resistance syndrome (UARS). In a study conducted by Rybczynski et al., half of the MFS events were central apneas rather than obstructive events.[25] In the study by Bobcock et al., for example, they assessed for UARS and found 59 individuals or 9.9% to have the disorder. Primary snoring occurred in 27 individuals representing 4.5%.[10]

Although there is clearly a higher prevalence of OSA among patients with hypermobility syndrome, more controlled studies are needed. The use of standardized polysomnography measures and grading as well as detailed assessment of craniofacial, chest, and subtype of the disorder should be conducted. Longitudinal studies following individuals with hypermobility syndrome from an early age would be helpful in better identifying the developmental course of OSA in this population, including typical ages of onset. Given the low prevalence of EDS and MFS, multisite studies that pool data across individuals are needed to better identify potential risk factors for OSA among individuals with hypermobility disorders. Clinicians in the care of patients with hypermobility syndrome should specifically ask for OSA-related symptoms (eg, fatigue, daytime sleepiness, etc.), even when the patient does not have obesity and other known risk factors are not present. It remains controversial as to whether there is a need of performing polysomnography in this population as a standard of practice for all cases, even with the lack of OSA signs and symptoms. This is especially significant given the lack of self-reported measures such as EDS not being related to OSA presence or its severity.[25] In addition, although home sleep studies are increasingly used for adults, such studies could miss a significant number of OSA cases among the hypermobility group.[10] Highlighting and monitoring compliance to the treatment of OSA to individuals in whom hypermobility syndrome has been diagnosed appear to be essential in this population and might prevent fatal cardiovascular complications.

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